SmithKline Beecham
Pharmaceuticals

October 28, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. **99D-2729**; Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products – General Considerations
Federal Register, September 3, 1999 (64FR171)

Dear Sir/Madam:

The draft guidance, according to the Notice issued at the time of the publication is intended to provide recommendations for sponsors and applicants intending to submit bioavailability (BA) and /or bioequivalence (BE) information in investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their amendments and supplements to CDER. The draft guidance provides general information on how to comply with the BA and BE requirements for orally administered dosage forms in 21 CFR part 320.

GENERAL COMMENTS:

SmithKline Beecham supports the PhRMA position manuscript on the topic of population and individual bioequivalence which will be published in the Journal of Clinical Pharmacology. As these proposals move forward SmithKline Beecham would strongly encourage the FDA to consider the PhRMA position manuscript in crafting improved versions of this draft guidance .

Detailed specific comments on the draft guidance are attached.

Sincerely,

Thomas M. Hogan
Director
North America Regulatory Affairs

Attachment
99D-2729

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1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917 7000. Fax (610) 917 7707.

SmithKline Beecham Comments on Draft FDA Guidances

The following 2 draft guidances have been reviewed:

1. BA and BE Studies for Orally Administered Drug Products - General Consideration

2. Average, Population, and Individual Approaches to Establishing Bioequivalence

General Comment applicable to both guidances

SmithKline Beecham supports the PhRMA position manuscript on the topic of population and individual bioequivalence which will be published in the Journal of Clinical Pharmacology (a copy may be obtained by contacting Nevine Zariffa, PhRMA BioStats at 215-814-1448). Additional comments on draft FDA guidances are presented below.

Comments on "BA and BE Studies for Orally Administered Drug Products - General Consideration"

II. Background

p.4, B. Bioavailability, para 2, 1st sentence: "From a pharmacokinetic (PK) perspective, BA data **for a given formulation** provide an estimate of the fraction of the orally administered dose that is absorbed **into the** systemic circulation..".

p.4, B. Bioavailability, para 3, 1st sentence : It is difficult to see how bioavailability (BA) studies *per se* would provide information about "..permeability and the influence of presystemic metabolism and p-glycoprotein or other transporters". The wording should be modified to suggest that BA studies might provide information about whether or not there may be issues associated with one or other of these processes.

p.5, C. Bioequivalence, general comment: It is well known that estimates of variance components in small crossover designs are imprecisely characterized; thus it is possible that increases in test variance may be observed by chance alone. The guidance should note this and indicate that sponsors may want to consider

reformulating following confirmation (in vitro or in vivo) of the increase in test product variance.

p.6, C. Bioequivalence, 1. IND/NDAs, para 2, 1st sentence: "....or lower than the reference product **and outside the BE acceptance range."** Also, the Agency may want to stress here that this only applies to INDs and NDAs, where prescribability and not switchability, is an issue.

p.6, C. Bioequivalence, 1. IND/NDAs, para 3, 1st sentence: "....a drug product **does not** perform~~ing as well as less optimally than~~ the reference product."

III. Methods to Document BA and BE

p.7, A. Pharmacokinetic Studies, 1. General Considerations: Methods to Document BA/BE, A: 2. Recommendations relating to pooling of data from a pilot study into a pivotal study (e.g. using a group sequential or alternative technique) should be considered.

p. 8, A. Pharmacokinetic Studies: A section on the use of interim statistical analyses would be useful.

p.8 , A. Pharmacokinetic Studies, 4. Replicate Study Designs: In line with the PhRMA position accepted by the FDA Advisory Committee, the guidance should stress the option to retain two treatment, non-replicate designs for ABE when appropriate to the study objective. Until further notice, i.e. until Pop BE/IBE methodologies have been properly evaluated and the guidance on the appropriate statistics finalised, the use of replicate designs should remain optional.

p.8 , A. Pharmacokinetic Studies, 5. Study Population: Please note that this section is not in agreement with CPMP and ICHA. A cautionary statement should be added noting that increasing the heterogeneity of the study population will impact study design. Increasing the heterogeneity may inflate the residual variability for average BE assessment in replicate designs as between-subject variability for the test and reference formulations may be increased. There should not be a rigid specification of the types of subjects that must be used.

p.9, A. Pharmacokinetic Studies, 8. Pharmacokinetic Measures of Systemic Exposure, a) Early Exposure: The partial AUC parameter, recommended for assessment of early exposure, is likely to be more variable than Cmax and subject

to the same potential source of error as other measures of rate of absorption. The high variability can complicate any assessment using an unscaled average bioequivalence procedure. Furthermore, to our knowledge, use of this criteria is not well established and is still under study. Market access should not be granted using a criteria that is under study.

p.10, B. Pharmacodynamic Studies, 2nd sentence: It should be noted here that PD studies can be appropriate, for an orally administered drug product delivering drug to the systemic circulation, if there is not a viable analytical method to measure drug exposure.

p. 10., D. In Vitro Studies, 3rd sentence: "....changes to approved NDAs and ANDAs."

p. 10,. In Vitro Studies: It should be noted that the FDA is not in agreement with the ICH regarding the allowance of disintegration testing instead of dissolution testing for certain defined (highly soluble active) products.

IV. Comparison of BA Measures in BE studies

Please refer to the Pharma position paper for comments pertaining to this section.

V . Documentation of BA and BE

p.13, 1st paragraph in Section V: It is not clear whether linear pharmacokinetics are required in order to obtain a wavier of in vivo studies for different strengths.

p.13, C. Immediate-Release Products: Capsules and Tablets: The option for dosing in the fed state should be included in this section.

p.13, C. Immediate-Release Products: Capsules and Tablets, 1. General Recommendations: The narrow window of 90-111 sets up a definition of narrow therapeutic drugs as those drugs for which greater than a 10% change in exposure can be of clinical significance. This definition is too narrow, and may not apply to all drugs that are currently labelled as having a narrow therapeutic range. We believe that the bioequivalence criterion needs to be drug-specific for narrow therapeutic window drugs. There may be some narrow therapeutic index drugs for which ± 10% is too wide a margin and others for which ± 20% is acceptable. The

definition of a narrow therapeutic drug should be sponsor defined on a case by case basis.

In addition, the narrow window creates a conflict with the draft drug interaction guidance. In that guidance, it is suggested that if bioequivalence is demonstrated with a probe substrate, then the sponsor does not have to worry about interactions involving the enzyme studied. For example if equivalence is demonstrated with caffeine, a CYP1A2 probe, then the sponsor can conclude that their drug will not affect CYP1A2, and no additional drug interaction studies with CYP1A2 substrates are needed. However, the current guidance implies that an analysis performed with a 20% window could not be extrapolated to narrow therapeutic window drugs.

p.13, C. Immediate-Release Products: Capsules and Tablets, 1. Exposure Measurements: Please see comment presented above regarding text of page 9 concerning the use of partial AUC as a measure of early exposure. The guidance states that if early exposure measurement is used, statistical analysis of Cmax is not needed. The implication is that early exposure is the more sensitive, discriminating parameter, though it is not clear that this is supported by the available data.

p.16, D. Modified Release Products, 1. NDAs: Under recommended studies, it should be stated that each dosage strength does not have to be referenced against an immediate release product at the same dosage strength and that an appropriate choice of a single reference dose is permissible.

p.16, D. Modified Release Products, 1. NDAs and 2 ANDAs: It is not clear why multiple dose studies are required for NDAs, but not for ANDAs.

VI. Special Topics

If the Agency has specific guidance regarding drugs that display non-linear PK, it should be presented in this section.

p.19, B. Moieties to be Measured, 1. Parent Drug Versus Metabolites, para 1: "Active moiety and active metabolites" should be defined up front. Further down the page a definition is given which seems appropriate: "..the absorbed degradant and/or metabolite contributes meaningfully (e.g. > 20% of total activity) to the safety and/or efficacy of the administered drug product".

p.19, B. Moieties to be Measured, 1. Parent Drug Versus Metabolites, para 1: This section should comment on how the data are to be assessed for bioequivalence. Often, bioequivalence of each component is assessed individually. However, particularly in the case in which there is significant inter-subject variation in the drug/active metabolite ratio and these components have different potencies, it may be argued that the proper comparison, between test and reference product, is that based on the sum, for all active components, of the products of the systemic exposures and the potencies.

p.19, B. Moieties to be Measured, 1. Parent Drug Versus Metabolites: It is not clear whether the parent or metabolite should be assayed when the parent is inactive and the metabolite is active and not formed via presystemic metabolism.

p.20, Enantiomers v Racemates, last sentence: Should read "....both enantiomers **separately**."

p.20, C. Long half-life drugs:

p.20, C. Long half-life drugs: The purpose of the last sentence of this section is not clear. It appears that the guidance is presenting alternative approaches for low and high variability drugs, but how the approaches differ is not obvious from the text. In addition, the method of truncation (e.g. AUC(0-t), AUC(0-t') should be discussed. Specifically, there is no mention in the guidance of the use of AUC(0-t') where t' is the latest time at which concentrations are quantifiable in all profiles for a subject. This section needs clarification.

p.21, D. First Point Cmax, last sentence: Should read "...even when ~~**the first time point is**~~ the highest observed concentration **occurs at the first time point.**"

p.21, F. Narrow Therapeutic Range Drugs: Please see comments above for p. 13, C. Immediate-Release Products: Capsules and Tablets, 1. General Recommendations.

p.24, Appendix 2: General PK Study Design, Subjects with predose plasma concentrations: The guidance should state whether the contribution of predose concentrations should be subtracted from Cmax and AUC using accepted PK methodologies. In addition, we agree that generally, if predose concentrations are greater than 5 % of Cmax , then the subject should be dropped from evaluations.

However, it should be noted that this procedure can exclude subjects exhibiting substantial evidence of carryover. While such a factor may complicate the analysis, there may be cases where such data can be taken into account. In some cases, deletion of subjects with predose plasma concentrations from the data set may bias inference (by failing to capture observations relating to unusual subjects) and may reduce the overall power of the study.

p.24, Appendix 2: General PK Study Design, Pharmacokinetic information recommended for submission, bullet 5: Clarification is required on the meaning of the term "Statistical Information" in this context. Presumably, the FDA are not asking for a statistical comparison between treatments for all these parameters (e.g. AUC(0-t)/AUC(0-inf) only tells us about the extent of extrapolation). It is also not clear what the Agency will do with these data. Many of the parameters listed have no impact on the determination of bioequivalence and should therefore not be required by the Agency. Please clarify this bullet to indicate where for which endpoints formal statistical procedures for the assessment of bioequivalence should be performed (lnAUC, lnCmax) and where summary statistics and/or nonparametric analysis (Tmax) are the minimum required.

Comments on "Average, Population, and Individual Approaches to Establishing Bioequivalence"

p. 9. V. Study Design, C. Sample Size and Dropouts: The wording relating to the inclusion of new subjects following dropouts should be altered to be more flexible since the potential for dropouts is greater in replicate design studies

p. 10, Statistical Analysis, A. Logarithmic Transformation, 1. General Procedures: 1. Procedures to account for gross departures from normality should be considered in the statistical analysis, and if appropriate following review with CDER, inference should be adapted accordingly. It should be noted that such departures may be due to chance or may truly be indicative of subpopulations in the study.

p. 10, Statistical Analysis, A. Logarithmic Transformation, 2. Presentation of Data: It has been well established (Westlake, 1988) that PK endpoints are generally lognormally distributed, implying that standard measures of centrality such as the arithmetic mean and SD (and the CV as described currently in text) may describe the data in an inappropriate manner. Geometric means and CV calculated in manner appropriate to the lognormal data should be provided according to the formula:

geometric mean = exp(arith. mean on $\log_e$ scale)

between-subject $CV_b(\%)$ = SQRT(exp(SD on $\log_e$ scale)^2 – 1) x 100

p. 12, Statistical Analysis, B. Data Analysis, 2. Population Bioequivalence, b. Nonreplicated Crossover Designs: Please clarify why a method of moments based approach is not also acceptable in situations where missing data is negligible. This would appear to be inconsistent with the approach adopted for the assessment of population and individual bioequivalence.

p. 12, Statistical Analysis, B. Data Analysis: It should be noted in this section that REML methods should be considered when missing data are included in statistical analysis.

p. 13, Statistical Analysis, B. Data Analysis, 2. Population Bioequivalence, c Replicated Crossover Designs: The wording of this section is inconsistent with the estimation procedure described in appendix F and is incorrect. It should be reworded to be consistent with appendix F or removed.

In replicate designs, it is known that between-subject and within-subject method of moment variances are dependent (between is estimated as a function of within, see Chinchilli 1996). The Cornish-Fisher expansion approach described in the appendix F is valid under the assumption that variance components involved are independent, and the estimation procedure for variances/covariances and the

subsequent method of BE assessment using the C-F expansion must take this into consideration.

p. 14, VII. Miscellaneous Issues: The potential for interim analysis should be addressed to allow, in replicate design studies, the potential to adjust sample size calculations

p. A-3, Appendix A: It has been established that the magnitude of estimates for subject-by-formulation variance are dependent on the magnitude of within-subject variability. The standard for allowable EI should take this into account.

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